

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Axel ULLRICH et al.
Title: USE OF ORGANIC COMPOUNDS FOR THE
INHIBITION OF FLK-1 MEDIATED
VASCULOGENESIS AND ANGIOGENESIS

Prior Appl. No.: 08/193,829

Prior Appl. Filing Date: February 9, 1994

Examiner: Unassigned

Art Unit: Unassigned

CONTINUING PATENT APPLICATION
TRANSMITTAL LETTER

Commissioner for Patents
Box PATENT APPLICATION
Washington, D.C. 20231

Sir:

Transmitted herewith for filing under 37 C.F.R. § 1.53(b) is a:

☒ Continuation ☐ Division ☐ Continuation-In-Part (CIP)

of the above-identified copending prior application in which no patenting, abandonment, or termination of proceedings has occurred. Priority to the above-identified prior application is hereby claimed under 35 U.S.C. § 120 for this continuing application. The entire disclosure of the above-identified prior application is considered as being part of the disclosure of the accompanying continuing application and is hereby incorporated by reference therein.

☒ Amend the specification by inserting before the first line, the following sentence: --This application is a continuation of U.S. App. Ser. No. 08/965,598, filed November 6, 1997, and a continuation of U.S. App. Ser. No. 08/193,829, filed February 9, 1994, now U.S. Pat. No. 6, 177,401, which is a continuation-in-part of U.S. App. Ser. No. 08/038,596, filed March 26, 1993, now abandoned, which is a continuation-in-part of U.S. App. Ser. No. 07/975,750, filed November 13, 1992, now abandoned.--

☐ Applicant claims small entity status under 37 CFR 1.27.

Enclosed are:

☒ Specification, Claim(s), and Abstract (85 pages).

☒ Informal drawings (25 sheets, Figures 1-17).

☒ Unexecuted Declaration and Power of Attorney (2 pages).

The filing fee is calculated below:

	Claims As Filed		Included in Basic Fee		Extra Claims		Rate		Fee Totals
Basic Fee							\$710.00		\$710.00
Total Claims:	51	-	20	=	31	x	\$18.00	=	\$558.00
Independents:	16	-	3	=	13	x	\$80.00	=	\$1,040.00
If any Multiple Dependent Claim(s) present:						+	\$270.00	=	\$270.00
Surcharge under 37 CFR 1.16(e) for late filing of Executed Declaration and late payment of filing fee						+	\$130.00	=	\$130.00
							SUBTOTAL:	=	\$2,708.00
<input type="checkbox"/> Small Entity Fees Apply (subtract 1/2 of above):								=	\$0.00
							TOTAL FILING FEE:	=	\$2,708.00

☐ A check in the amount of \$0.00 to cover the filing fee is enclosed.

☒ The required filing fees are not enclosed but will be submitted in response to the Notice to File Missing Parts of Application.

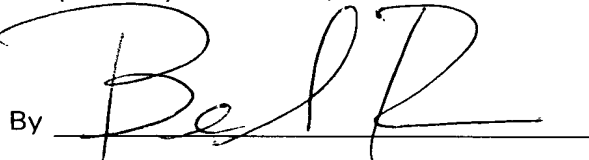
☐ The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741.

Please direct all correspondence to the undersigned attorney or agent at the address indicated below.

Date 1/23/01

FOLEY & LARDNER
Washington Harbour
3000 K Street, N.W., Suite 500
Washington, D.C. 20007-5109
Telephone: (202) 672-5475
Facsimile: (202) 672-5399

Respectfully submitted,

By 

Beth A. Burrous
Attorney for Applicant
Registration No. 35,087

Flk-1 IS A RECEPTOR FOR VASCULAR
ENDOTHELIAL GROWTH FACTOR

5	TABLE OF CONTENTS	<u>Page</u>
	1. <u>INTRODUCTION</u>	1
10	2. <u>BACKGROUND OF THE INVENTION</u>	1
	3. <u>SUMMARY OF THE INVENTION</u>	3
	4. <u>BRIEF DESCRIPTION OF THE FIGURES</u>	4
15	5. <u>DETAILED DESCRIPTION OF THE INVENTION</u>	9
	5.1. <u>THE Flk-1 CODING SEQUENCE</u>	12
	5.2. <u>EXPRESSION OF Flk-1 RECEPTOR AND</u>	
20	<u>GENERATION</u>	
	<u>OF CELL LINES THAT EXPRESS Flk-1</u>	16
	5.2.1. <u>EXPRESSION SYSTEMS</u>	17
	5.2.2. <u>IDENTIFICATION OF TRANSFECTANTS</u>	
	<u>OR TRANSFORMANTS THAT EXPRESS</u>	
25	<u>THE Flk-1</u>	24
	5.3. <u>USES OF THE Flk-1 RECEPTOR</u>	
	<u>AND ENGINEERED CELL LINES</u>	26
	5.3.1. <u>SCREENING OF PEPTIDE LIBRARY</u>	
	<u>WITH Flk-1 PROTEIN OR</u>	
30	<u>ENGINEERED CELL LINES</u>	28
	5.3.2. <u>SCREENING OF ORGANIC COMPOUNDS</u>	
	<u>WITH Flk-1 PROTEIN OR ENGINEERED</u>	
	<u>CELL LINES</u>	30
	5.3.3. <u>ANTIBODY PRODUCTION AND</u>	
35	<u>SCREENING</u>	34

		<u>Page</u>
	5.4. <u>USES OF Flk-1 CODING SEQUENCE</u>	36
	5.4.1. <u>USE OF Flk-1 CODING SEQUENCE</u> <u>IN DIAGNOSTICS AND THERAPEUTICS</u>	37
5	5.4.2. <u>USE OF DOMINANT</u> <u>NEGATIVE</u> <u>Flk-1 MUTANTS IN GENE THERAPY</u>	40
	5.5. <u>USE OF Flk-1 RECEPTOR OR LIGANDS</u>	43
10	48
	6. <u>EXAMPLE: CLONING AND EXPRESSION PATTERNS</u> <u>OF Flk-1, A HIGH AFFINITY RECEPTOR FOR VEGF</u>	50
	6.1. <u>MATERIALS AND METHODS</u>	51
15	6.1.1. <u>cDNA CLONING OF Flk-1</u>	51
	6.1.2. <u>MOUSE EMBRYOS</u>	51
	6.1.3. <u>PREPARATION OF PROBES</u>	52
	6.1.4. <u>RNA EXTRACTION AND</u> <u>NORTHERN ANALYSIS</u>	52
20	6.1.5. <u>IN SITU HYBRIDIZATION</u>	53
	6.1.6. <u>PREPARATION OF ANTISERA</u>	53
	6.1.7. <u>TRANSIENT EXPRESSION</u> <u>OF Flk-1 IN COS-1 CELLS</u>	54
	6.1.8. <u>RADIOIODINATION OF VEGF</u>	55
25	6.1.9. <u>CROSSLINKING OF VEGF TO Flk-1</u>	55
	6.1.10. <u>VEGF BINDING</u>	56
	6.1.11. <u>RETROVIRAL VECTORS ENCODING</u> <u>TRANSDOMINANT-NEGATIVE MUTANTS</u> <u>OF Flk-1</u>	57
30	6.1.12. <u>THE CAPABILITY OF FLK-1 TM TO</u> <u>FORM</u> <u>SIGNALLING-INCOMPETENT HETERODIMERS</u>	57
35	6.1.13. <u>INTRACEREBRAL GRAFTING</u>	

		<u>Page</u>
	<u>OF GLIOMA CELLS</u>	61
5	6.1.14. ASSAY FOR AND IDENTIFICATION OF ORGANIC COMPOUNDS THAT MODULATE <u>FLK-1 MEDIATED SIGNAL TRANSDUCTION</u>	63
	6.1.15. SYNTHESIS OF A 3-PHENYL-1, <u>4-DIAZA-ANTHRACENE</u>	64
	6.2. <u>RESULTS</u>	64
10	6.2.1. <u>ISOLATION OF Flk-1</u>	64
	6.2.2 EXPRESSION OF Flk-1 mRNA <u>DURING EMBRYONIC DEVELOPMENT</u> . . .	65
	6.2.3. EXPRESSION OF Flk-1 <u>DURING ORGAN ANGIOGENESIS</u>	67
15	6.2.4. Flk-1 EXPRESSION IN <u>ENDOTHELIAL CELL PROGENITORS</u> . .	68
	6.2.5. Flk-1 IS A HIGH AFFINITY <u>RECEPTOR FOR VEGF</u>	68
20	6.2.6. INHIBITION OF TUMOR GROWTH BY TRANSDOMINANT-NEGATIVE <u>INHIBITION OF Flk-1</u>	70
	6.2.7. IDENTIFICATION OF AN ORGANIC COMPOUND THAT INHIBITS FLK-1 <u>RECEPTOR PHOSPHORYLATION</u>	72
25		
30		
35		